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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,675	07/09/2001	Olga Bandman	PF-0531 USN	8931

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EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,675	BANDMAN ET AL.	
	Examiner	Art Unit	
	Prema M Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-62* is/are pending in the application.

4a) Of the above claim(s) *52-53, 55-57, 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-51,54,58,59,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/10/2004 has been entered.

Claims 1-43 have been canceled previously. Currently amended claims 44, 51, 61, (11/10/04), previously pending claims 45-50, 54, 58-59, 61-62, are pending in the instant application. Claims 52-53, 55-58, 60,

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC §§ 101 and 112, first paragraph

3. Claims 44-51, 54, 58-59, 61-62 are rejected under 35 U.S.C. 101.

This rejection is maintained for reasons of record set forth at pages 3-7 of the previous Office action (3/18/04) and pages 2-5 of the previous Office action 7/13/2004.

Applicants argue that the claimed protein has a function with biological significance based on Sugiomto et al. and Hsu et al. Specifically, Applicants argue that the claimed protein (which is identical to p34SEI1 and TRIP-BrI) antagonizes p16INK4a, which inhibits CDK4 and CDK6, as well as regulates E2F-1/DP-1 transcriptional activity. However, contrary to Applicants arguments, these specific CDK's are not

recited in the instant specification. There are over 30 species of CDKs. The specification only recites that:

Chemical and structural homology exists between CECRP and cell cycle regulation proteins. In addition the expression of CECRP is closely associated with cell proliferation. Therefore, in cancers or immume disorders where CECRP is an activator, or enhancer, and is promoting cell proliferation, it is desirable to decrease the expression of CECRP. In cancers or immune disorders where CECRP is an inhibitor or suppressor of cellular processes that modulate cell proliferation it is desirable to provide the protein or to increase the expression of CECRP.

There is no disclosure in the instant specification of the percent homology between the instant CECRP protein and other cell cycle regulation proteins. It is a mere assertion by Applicants that the instant CECRP protein has homology to other cell cycle regulation proteins. Furthermore, Applicants argue that the expression of the claimed protein would specifically relate to the types of cancers listed in the specification at page 40, lines 7-11, which recites that:

Polynucleotide sequences encoding CECRP may be used for the diagnosis of a disorder associated with expression of CECRP. Examples of such a disorder include, but are not limited to, actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone

marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

Contrary to Applicants arguments, Applicants have failed to demonstrate differential expression of the CECRP protein between normal and any of the recited cancerous tissues. Applicants specifically recite on page 40, lines 4-5 that "examples of such disorder include, but are not limited to...".

Applicants argue that the Tang et al 2002 publication confirms that SEI-1 is associated with cell proliferation and cell cycle control. There is no nexus between the candidate oncogene SEI-1 (within a minimal amplified region at 19q13.1 in ovarian cancer cell lines) and the claimed CERRP protein. The last 2 lines of the abstract of the Tang et al reference recites that "the proliferation-related function of AKT2 and SEI-1 suggests that both genes are likely to be biological targets of an amplification event at 19q13.1 in ovarian cancer and to play important roles in ovarian tumorigenesis". Furthermore, overexpression of genes in cancer cell lines is not comparable to overexpression of genes in organ cancers.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. Until some actual and specific significance can be attributed to the protein identified in the specification as "having homology to cell cycle regulation proteins" the instant invention is incomplete. In the absence of knowledge of the biological significance of the instant protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the treatment or prevention of ovarian cancer as well as in the diagnosis of ovarian

cancer is not a specific or substantial utility and does not support patentability. Since the instant specification does not disclose a credible "real world" use for the instant protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

Claims 44-51, 54, 58-59, 61-62 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantially asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The instant specification does not disclose a biological activity for the claimed protein, therefore, there is no specific and substantial asserted utility or well established for the claimed protein.

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 44-51, 54, 58-59, 61-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a polypeptide of SEQ ID NO:3 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to "naturally occurring amino acid sequence at least 95%

identical to the amino acid sequence of SEQ ID NO:3" as recited for example in claim 44(b).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The structures of naturally occurring sequences at least 95% identical to the amino acid sequence of SEQ ID DNO:3 are not defined. With the exception of SEQ ID NO:3, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides or polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for protein and nucleic acid variants is provided in the specification on pages 9-10. However, no disclosure, beyond the mere mention of variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated nucleic acid molecule comprising a nucleic acid sequence consisting of SEQ ID NO:8 and a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:3 and equivalent degenerative codon sequences thereof, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

4b. Claims 44-51, 54, 58-59, 61-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:3 and the polypeptide encoded thereby, does not reasonably provide enablement for an isolated a naturally occurring polynucleotide at least 95 % identical to SEQ ID NO:8 or an isolated a naturally occurring polypeptide at least 95 % identical to SEQ ID NO:3. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 44, for example, is overly broad in the recitation of "at least 95% identical to the amino acid sequence of SEQ ID NO:3" since no guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the desired characteristics. Variants of the polynucleotide can be generated by conservative or nonconservative changes, allelic, splice species or polymorphic variants, arising by natural deletions additions or substitutions. However, no actual or prophetic examples on expected performance parameters of any of the possible muteins of SEQ ID NO:3 have been disclosed in the instant specification (pages 9-10). There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid sequence encoding a polypeptide other than that exemplified in the specification. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the

guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Applicants argue that Table 2 of the instant specification recites various structural and functional fragments of SEQ ID NO:3 such as

(1) potential phosphorylation sites (at 544, S60, 598, S1 17, S123, S180 and 7-73) and (2) identifying sequences and/or structural motifs such as the inhibin beta chain signature sequence. Applicants believe that Table 2 accordingly discloses those structural elements that are critical to encoding a functional polypeptide. As such, a skilled artisan would be able to create functionally equivalent 95% identical polypeptides by following the teachings of the specification. Specifically, by using the information from Table 2, one of ordinary skill would know to retain those portions of the sequence identified in Table 2 when creating a variant 95% identical to SEQ ID NO: 3.

However, contrary to Applicants arguments, the issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and In re Wands, 8USPQ2d, 1400 (CAFC 1988). If Applicants will kindly review page 1404 of In re Wands, they will find that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the

nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. Applicants arguments that the standard is that of mutating a subject protein and testing to see if it retains the desired biological activity is a position that has been routinely dismissed by the courts, as shown by the decisions cited above. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues of the naturally-occurring protein sequences, which are required for functional and structural integrity of the protein. It is this additional characterization of the disclosed protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Furthermore, Applicant is encouraged to review the discussion of 35 U.S.C. § 112, first paragraph, in a recent CAFC decision, Genentech, Inc. v. Novo. Nordisk, 42 USPQ2d, 100 (CAFC 1997), in which the decisions in In re Fisher, Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., and In re Wands were considered as the controlling precedents in determining enablement issues where protein and recombinant DNA issues are concerned. These decisions have been relied upon in the instant rejection and by the Court because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one

can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not, without actually making and testing them, then the instant application does not support the breadth of the claims. In the instant case it is highly improbable that any protein having 95% amino acid sequence identity to the disclosed protein will more likely than not perform in the manner disclosed and the instant specification does not provide the guidance needed to predictably alter the sequences with any reasonable expectation that the resulting protein will have the desired activity. Therefore Applicants have not presented enablement commensurate in scope with the claims.

Claim rejections-35 USC § 112, second paragraph

5. Claims 44-51, 54, 58-59, 61-62 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44, 51, 61-62 are indefinite in the recitation of the term "naturally occurring". It is unclear whether this term imposes a required limitation on the claim, such that it only encompasses, for example, nucleic acid molecules amplified from cDNA or all nucleic acid molecules that encode the polypeptide. Therefore, the metes and bounds of the claim are unclear.

Claims 44, 51, 61-62 are rejected for reciting "polypeptide promotes cell proliferation". It is unclear in which cells proliferation is induced by the claimed polypeptide.

Claim 41(c), line 3, and claim 62, line 8, are rejected for reciting "polypeptide promotes cell proliferation". It is unclear whether the "polypeptide" claimed or the "polypeptide fragment" claimed promotes cell proliferation. Furthermore, the metes and bounds of the limitation "fragment of the amino acid sequence of SEQ ID NO:3"are unclear because a single amino acid encompasses a "polypeptide fragment" and meets the limitations of this claim.

Claim 51© recites "having cell cycle regulating activity". It is unclear from this limitation if the polypeptide up or down regulates the cell cycle.

Claims 45-49, 54, 58-59 are rejected as vague insofar as they depend on the above rejected claims for their limitations.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44, 46, 49-50, 58, 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Genetics Institute Inc. (WO 92/05256).

WO 92/05256 discloses a cDNA encoding the 40 kD subunit of natural killer cell stimulatory factor, which is a secreted protein (see pages 17-20, Table I). Therefore, the

DNA encoding a fragment of the NKSF 40 kD polypeptide of the reference, would potentially be a single amino acid (meets fragment limitation of claims 44, 62). The reference also discloses that the cDNA encoding the polypeptide was cloned into the expression vector pXM for COS expression (page 47, lines 13-17), as shown by the ability of the vector to be expressing functional protein which was obtained in a pharmaceutically acceptable carrier (pages 50-60, 42-43). Therefore, the cDNA and polypeptide disclosed in the reference meets the limitations of claims 44, 46, 49-50, 58, and 62.

Conclusion

No claim is allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
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